

Claims 58, 61, 63 and 71-73 have been amended to more particularly point out that the claimed method is for removing one or more artifacts from a measured biological response profile which comprises *measurements of a plurality of cellular constituents in a biological sample in response to a perturbation* (emphasis added). Support for the amendments is found in the specification at page 9, lines 8-13 and lines 20-32; page 10, lines 21-25; and page 74, lines 8-32.

Claims 58 and 71-72 have also been amended to more particularly point out that each of said one or more artifacts comprises *a artifact pattern comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values* (claim 58) or *changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values* (claims 71-72) (emphasis added). Claims 71-72 have further been amended to more particularly point out that the artifact template comprises artifact signature having greatest similarity to said biological response profile. Support for the amendments is found in the specification, e.g., at page 34, line 23 through page 36, line 1; and page 74, lines 8-32.

Claims 58 and 71 have also been amended to include the recitation of a final process step, i.e., the phrase "thereby removing said one or more artifacts from said measured biological response profile," at the end of the claims so that the last lines of the claims agree back with the preamble of the claims.

Claim 59 has been amended to more particularly point out that each of the one or more artifact patterns *comprises changes in amplitudes of measurements of said cellular constituents associated with the artifact to which the artifact pattern corresponds* (emphasis added). Support for the amendment is found in the specification at page 34, lines 23-25 and page 35, lines 10-23.

Claim 60 has been amended to recite that each of the one or more artifact patterns is determined by experiments with perturbations of *said one or more experimental variables* to which the artifact pattern corresponds (emphasis added). Support for the amendment is found in the specification, e.g., at page 35, lines 6-8 and page 74, lines 16-22.

Claim 61 has also been amended to recite that the control biological response profiles comprise measurements of a plurality of cellular constituents *in experiments wherein said one or more experimental variables are perturbed to produce said artifact pattern* (emphasis

added). Support for the amendment is found in the specification at page 35, line 6-8 and page 74, lines 16-22.

Claims 63-64, 70 and 73-76 have been amended to delete the word "objective." Support for the amendments is found in the specification, e.g., at page 35, lines 15-23.

Claims 70 and 75-76 have been amended to more particularly point out that in the claimed method the *difference term associated with each cellular constituent in said function is weighted by a weighing factor* and the weighing factor is selected according to *the significance* of the measured value of said cellular constituent (emphasis added). Support for the amendments is found in the specification at page 35, lines 15-23.

Claims 71 and 72 have also been amended to more particularly point out that in the claimed methods each of the artifact signatures *comprises changes in amplitudes of measurements of said cellular constituents corresponding to different levels of said one or more experimental variables* (emphasis added). Claims 71 and 72 have further been amended to more particularly point out that an artifact template comprises artifact signature having greatest similarity to said biological response profile. Support for the amendments is found in the specification at page 35, lines 29-30; page 74, lines 16-22; and Fig. 19.

No new matter has been added by these amendments. Entry of the foregoing amendments and the following remarks are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH
SHOULD BE WITHDRAWN

Claims 58-64 and 70-76 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 58 and 71 are rejected as being indefinite for failing to recite a final process step which agrees back with the preamble. Applicants have amended the claims to include a final step which agrees back with the preamble. The rejections are therefore obviated and should be withdrawn.

Claims 58-64 and 70-76 are rejected as being indefinite for the use of the terms "artifact," "artifact pattern," "artifact template," and "artifact signatures." Applicants have amended claims 58 and 71-72 to more particular point out that an artifact comprises a artifact pattern comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values (claim 58) or changes in

measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values (claims 71-72), that an artifact pattern comprises changes in measurements of cellular constituents resulting from deviation of one or more experimental variables from desired values (claim 58), that an artifact template comprises artifact signature having greatest similarity to said biological response profile, and that artifact signatures comprise changes in amplitudes of measurements of said cellular constituents corresponding to different levels of said one or more experimental variables. Applicants submit that it will be clear to one ordinary skilled in the art what the terms refer to and how to determine them. The rejections are therefore obviated and should be withdrawn.

Claim 59 is rejected as being indefinite for reciting the phrase "knowledge of the variables." Applicants have amended the claim by deleting the phrase. The rejection is therefore obviated and should be withdrawn.

Claims 59-61 are rejected as being indefinite because of the recitation of "the respective artifact." Applicants have amended the claims by deleting the word "respective." The rejections are therefore obviated and should be withdrawn.

Claim 59 is rejected as being indefinite for reciting the term "relative." Applicants have amended the claim by deleting the term. The rejection is therefore obviated and should be withdrawn.

Claim 59 is rejected for reciting "[the]...relative amplitudes." Applicants have amended the claim by deleting the word "relative." The rejection is therefore obviated and should be withdrawn.

Claim 60 is rejected for reciting the phrase "suspected causative variable." Applicants have amended the claim by deleting the phrase. The rejection is therefore obviated and should be withdrawn.

Claims 63-64 and 70-76 are rejected as being indefinite for reciting the phrase "objective function." Applicants have amended the claims by deleting the word "objective." The rejections are therefore obviated and should be withdrawn.

Claim 70 is rejected as being indefinite for reciting the phrase "each cellular constituent's contribution." Applicants have amended the claim to more particularly point out that the difference term associated with each cellular constituent in said function is weighted by a weighing factor. The rejection is therefore obviated and should be withdrawn.

Claim 70 is rejected for reciting the limitation "the relative certainty or significance." The Examiner contends that there is insufficient antecedent basis for this limitation. Applicants have amended the claim to delete the phrase "relative certainty." Applicants submit that the significance of a measured value is well known in the art. The rejection is therefore obviated and should be withdrawn.

Claims 70 and 75-76 are rejected as being indefinite for reciting the term "relative." Applicants have amended the claims such that the term is no longer present. The rejections are therefore obviated and should be withdrawn.

Claims 71-72 are rejected as being indefinite for reciting the phrase "levels of severity." Applicants have amended the claims to recite that each of said artifact signatures comprises changes in amplitudes of measurements of said cellular constituents corresponding to different levels of said one or more experimental variables. The rejections are therefore obviated and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102(e)
SHOULD BE WITHDRAWN

Claims 58 is rejected under 35 U.S.C. § 102(e) as being anticipated by Garini et al., U.S. Patent No. 5,798,262 ("Garini"). The Examiner contends that Garini discloses a method which involves removing one or more artifact patterns from the biological profile (i.e., the measured fluorescence image of the mapped chromosomes) by background subtraction and internal reference normalization, which reads on the artifact/artifact patterns. Applicants respectfully disagree with the Examiner for reasons set forth below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

Garini discloses a method for classification of in situ painted chromosomes into a color karyotype and a method for identifying prominent internal reference spectra to effect such classification. In Garini, chromosomes, or portions thereof, of a cell are painted with multiple different fluorophores. Color images of the chromosomes are collected and analyzed to determined the identities of each chromosomes. Applicants respectfully point out

that the background subtraction taught by Garini involves subtraction from all pixels of background fluorescence signals common to all pixels by subtraction of a spectrum of a pixel or average spectrum of some or all pixels in the background region (see, Garini, column 23, lines 26-38), and the spectrum normalization taught by Garini involves dividing the intensity at each value by the integrated intensity of the whole spectrum (see, Garini, column 23, lines 12-25). Nowhere does Garini teach a measured *biological response profile* which comprises measurements of a plurality of cellular constituents in a biological sample *in response to a perturbation* or an artifact which comprises changes in measurements of cellular constituents resulting from deviation of one or more experimental variables from desired values, much less a method of removing one or more such artifacts from a measured biological response profile. Therefore, Applicants submit that Garini clearly does not anticipate the claimed method of the present invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (e) over Garini be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a)
SHOULD BE WITHDRAWN

Claims 58-64 and 70-76 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,798,262 ("Garini"). The Examiner contends that in Garini classification of the multi-spectral karyotype is carried out through a least squares minimization algorithm that removes/subtracts artifacts through an artifact pattern/template, and thus, Garini renders the invention as claimed by Applicants obvious. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, Garini discloses a method for classification of in situ painted chromosomes into a color karyotype and a method for identifying prominent internal reference spectra to effect such classification. In Garini, chromosomes, or portions thereof,

of a cell are painted with multiple different fluorophores. Color images of the chromosomes are collected and analyzed to determine the identities of each chromosome. In particular, in Garini, an observed image is compared to reference spectra in a library, e.g., by using a least squares minimization algorithm, to identify a reference spectrum which is most similar to the observed image (see, e.g., Garini, column 24, line 50 through column 25, line 34). In the methods of the present invention, on the other hand, an artifact pattern/template is *subtracted* from the measured biological response profile, e.g., by using a least squares minimization algorithm for determining the optimal scaling coefficients for removing/subtracting artifacts. Therefore, Garini fails to provide any hint or suggestion of the claimed invention. Garini does not teach or suggest removing one or more artifacts from a measured biological response profile which comprises measurements of a plurality of cellular constituents in a biological sample *in response to a perturbation*. Garini does not teach or suggest an artifact which comprises changes in measurements of cellular constituents resulting from deviation of one or more experimental variables from desired values. Nor does Garini teach or suggest a method for removing one or more artifacts from a measured biological response profile by subtracting an artifact template from the measured biological response profile, much less teach or suggest an artifact template which comprises an artifact signature which has greatest similarity to the measured biological response profile or teach or suggest obtaining such an artifact signature by comparing the measured biological response profile to a library of artifact signatures, each comprising changes in amplitudes of measurements of the cellular constituents corresponding to different levels of the one or more experimental variables. One of ordinary skill in the art would not be motivated to such methods with a reasonable expectation of success from the teachings of Garini. Therefore, the presently claimed invention is not made obvious by the cited reference. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition

for allowance. Withdrawal of the Examiner's rejections, and allowance of the application, are respectfully requested.

Respectfully submitted,

Date August 14, 2001

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures

EXHIBIT A: MARKED VERSION OF THE AMENDED CLAIMS

U.S. APPLICATION SERIAL NO. 09/220,275

(ATTORNEY DOCKET NO. 9301-039-999)

(as amended August 14, 2001)

58. (Twice Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents in a biological sample in response to a perturbation, each of said one or more artifacts comprising an artifact pattern comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising subtracting said one or more artifact patterns from the measured biological response profile, [wherein each of said one or more artifact patterns corresponds to an artifact,] thereby removing said one or more artifacts from said measured biological response profile.

59. (Twice Amended) The method of claim 58, wherein each of the one or more artifact patterns [is determined by knowledge of the variables that cause the respective artifact and] comprises changes in [relative] amplitudes of [responses] said measurements of said cellular constituents associated with the [respective] artifact to which the artifact pattern corresponds.

60. (Twice Amended) The method of claim 58, wherein each of the one or more artifact patterns is determined by experiments with perturbations of [suspected causative] said one or more experimental variables [of the respective artifact] to which the artifact pattern corresponds.

61. (Twice Amended) The method of claim 58, wherein each of the one or more artifact patterns is determined by a cluster analysis of control biological response profiles, the control biological response profiles comprising measurements of a plurality of cellular constituents in experiments wherein [the respective artifact to which the artifact pattern corresponds arises] said one or more experimental variables are perturbed to produce said artifact pattern.

63. (Twice Amended) The method of claim 62, wherein the scaling coefficients are determined by a method comprising determining the values of said scaling coefficients such that the value of [an objective] a function of the difference between the measured biological response profile and the sum of the one or more scaled artifact patterns is minimized.

64. (Twice Amended) The method of claim 63, wherein the [objective] function is minimized by a least squares minimization.

70. (Amended) The method of claim 63 or 64, wherein the difference term associated with each cellular [constituent's contribution to] constituent in said [objective] function is weighted by a weighing factor, wherein said weighing factor is selected according to the [relative certainty or] significance of the measured value of said cellular constituent.

71. (Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents in a biological sample in response to a perturbation, each of said one or more artifacts comprising changes in measurements of said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising subtracting an artifact template from the measured biological response profile, wherein said artifact template comprises an artifact signature having greatest similarity to said biological response profile and is obtained by a method comprising comparing said measured biological response profile to a library of artifact signatures, each of said artifact signatures comprising changes in amplitudes of measurements of said cellular constituents corresponding to different levels of [severity of artifacts] said one or more experimental variables, said comparing comprising pattern matching of said measured biological response profile against said library; thereby removing said one or more artifacts from said measured biological response profile.

72. (Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents in a biological sample in response to a perturbation, each of said one or more artifacts comprising changes in measurements of said

cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising: (a) comparing said measured biological response profile to a library of artifact signatures to generate an artifact template, each of said artifact signatures comprising changes in amplitudes of measurements of said cellular constituents corresponding to different levels of [severity of artifacts] said one or more experimental variables, said artifact template comprising an artifact signature having greatest similarity to said biological response profile, said comparing comprising pattern matching of said measured biological response profile against said library; and (b) subtracting said artifact template from said measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.

73. (Amended) The method of claim 71 or 72, wherein said comparing comprises minimizing [an objective] a function of the difference between said measured biological response profile and said library of artifact signatures.

74. (Amended) The method of claim 73, wherein said [objective] function is minimized by a least squares minimization.

75. (Amended) The method of claim 73, wherein the difference term associated with each cellular [constituent's contribution to] constituent in said [objective] function is weighted by a weighing factor, wherein said weighing factor is selected according to the [relative certainty or] significance of the measured value of said cellular constituent.

76. (Amended) The method of claim 74, wherein the difference term associated with each cellular [constituent's contribution to] constituent in said [objective] function is weighted by a weighing factor, wherein said weighing factor is selected according to the [relative certainty or] significance of the measured value of said cellular constituent.